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Introduction: Positron emission tomography (PET) is a central tool to study neurodegenerative diseases, allowing the measurement of hypometabolism and abnormal protein deposits (amyloid, tau). Modeling the spatiotemporal pattern of PET alterations in the cortex along the course of the illness is essential to understand disease progression and develop prognostic tools. In this study, we propose a generic method to model the spatiotemporal progression of PET alterations on the cortical surface from longitudinal images by combining two recently proposed approaches: i) a non-linear mixed-effects model for spatially distributed measurements based on Riemannian geometry (Koval et al, 2018; Schiratti et al, 2017); ii a method for projection of PET data onto the subject's cortical surface (Marcoux et al, 2018). The model can reconstruct spatiotemporal patterns of progression at both population and individual level. We applied this approach to study the progression of hypometabolism along the course of Alzheimer's disease (AD) from the prodromal stage.

Methods: Brain metabolic activity, mainly located within the cortex, is known to be altered during the course of Alzheimer's disease (AD). Surface-based approaches, such as the one developed by (Marcoux et al, 2018), are thus well suited to analyze cortical hypometabolism derived from FDG PET images. This method, part of the open-source Clinica software (Routier et al. 2018), includes i) co-registration of PET and T1-w MR images, ii) intensity normalization, iii) partial volume correction, iv) robust projection of the PET signal onto the subject's cortical surface, v) spatial normalization to a template.

The resulting projections once applied to repeated observations of multiples patients might inform about the spatiotemporal progression of the PET alterations. However, subjects are likely to be at different disease stages and to present different spatial patterns. (Koval et al, 2018) proposed to recombine the short-term individual observations to retrace the long-term history of the disease for spatially distributed data, while accounting for the inter-subject spatiotemporal variability. This model generates an average progression profile defined at each point of the cortical surface. Furthermore, subject's trajectories are characterized by individual variations of the mean evolution, specifically an age at disease onset, a pace of progression and a spatial pattern of alteration. They enable the reconstruction of individual trajectories and the estimation of the spatiotemporal variability in the population.

We applied our approach to study progression of cortical hypometabolism along the course of AD, starting from the prodromal stage. Specifically, mild cognitively impaired patients,

that progressed to AD during follow-up visits and that had at least two visits with both MRI and PET data, were selected from the ADNI database. This corresponds to 156 patients (74.0 ± 7.0 years, 89 males) with 4.4 visits on average (679 visits in total).

Results: Fig. 1 shows the metabolism decrease rate on the cortical surface for the mean profile of PET alterations. Greatest alterations are located in the precuneus, the parahippocampal gyrus, inferior and middle temporal gyri, and the inferior parietal lobule, followed by prefrontal regions. The sensory and visual cortices are spared.

The individual trajectories, considered as spatiotemporal variations of the average trajectories, allow the reconstruction of the observations. The mean relative error of reconstruction, uniformly distributed over the brain surface, is lower than 25%, except in areas close to the corpus callosum that are prone to poor preprocessing (Fig. 2.a). An example of a reconstruction is given on Fig. 2.b.

Conclusion: We proposed a new approach to model the progression of PET alterations. Application to AD demonstrated that the method unveils relevant patterns and can adequately reconstruct the trajectory of alterations at the individual patient level. It could become a useful tool for understanding progression of neurodegenerative diseases and build new prognostic systems.

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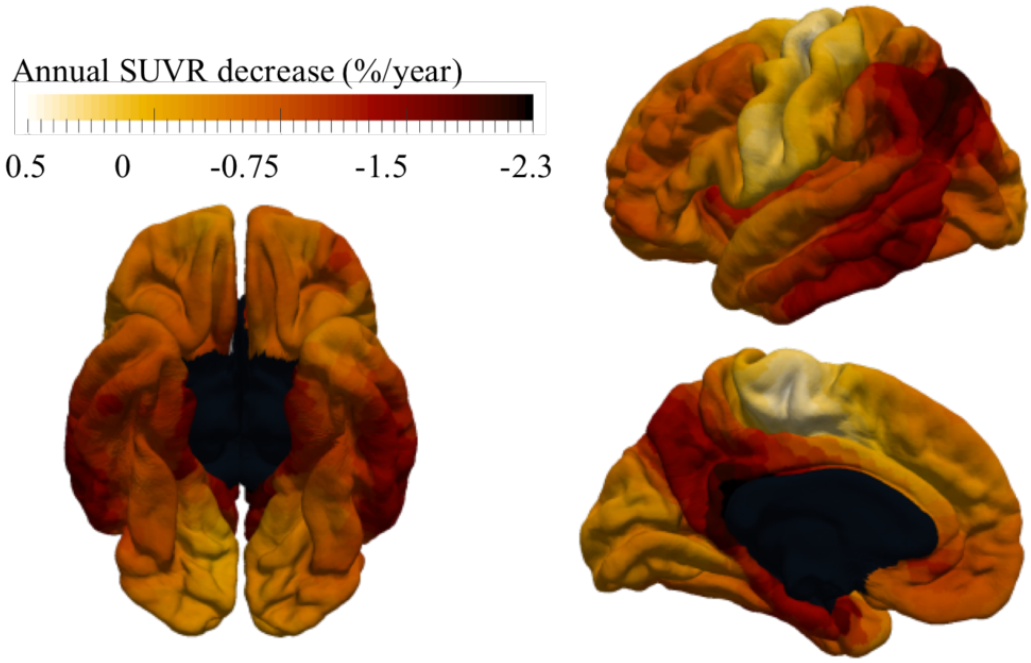

Figure 1: Map of the annual standard uptake value ratio (SUVR) decrease.

Figure 1

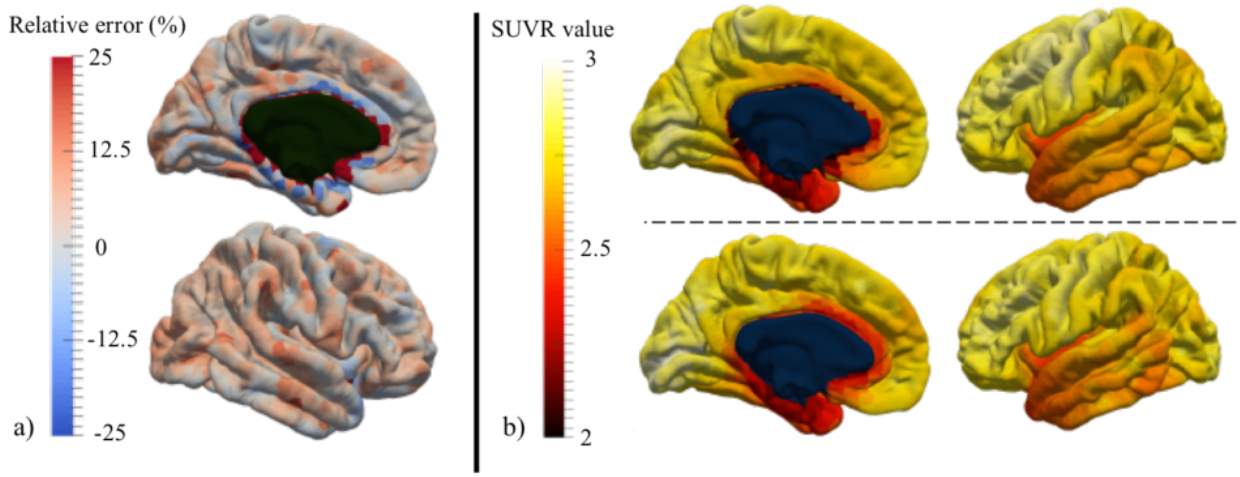

Figure 2 : The model is able to reconstruct the individual trajectories as spatiotemporal variations of the average trajectory. a) shows the mean relative error between the individual observations and their reconstructions, as illustrated on b) with a real observation (top) and its reconstruction (bottom).

Figure 2